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California  
Environmental  
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Agency



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Pesticide  
Regulation

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NOTICE OF COMPLETION OF RISK ASSESSMENT  
FOR THE PESTICIDE PRODUCT  
TALSTAR® T & O (Bifenthrin)

The Department of Pesticide Regulation (DPR) has completed a human health risk assessment on the use of the active ingredient bifenthrin under greenhouse conditions on nonfood crops.

Enclosed are copies of the final Risk Characterization and Exposure Assessment documents. Using current toxicity and exposure data, DPR finds that significant adverse effects could occur as a result of the use of Talstar® T & O in greenhouses. DPR needs to make a determination as to whether the risk can be mitigated.

Mitigation measures need to be developed to reduce exposure to:

- Greenhouse applicators and harvesters.

Please submit proposed mitigation measures to DPR. Submit the proposals in writing and within **90** days. Proposals received after 90 days may not receive consideration by DPR before finalization of the risk mitigation document. Please address all proposals to:

Risk Mitigation Proposals - (Talstar® T & O)  
Pesticide Registration Branch  
Department of Pesticide Regulation  
1020 N Street, Room 332  
Sacramento, California 95814-5624

If requested, DPR will schedule a meeting to discuss submitted mitigation proposals. When DPR determines what mitigation measures must be taken, you will be given an opportunity to voluntarily implement those measures. When completed, DPR intends to send you a copy of the Risk Mitigation document.



Pete Wilson  
*Governor*

James M. Strock  
*Secretary for  
Environmental  
Protection*

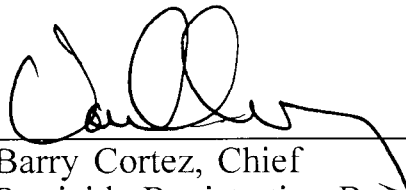
James W. Wells  
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NOTICE OF COMPLETION OF RISK ASSESSMENT -Talstar® T & O  
Page Two

Please address all requests for additional information to  
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Registration Branch, at (916) 324-3931.

  
\_\_\_\_\_  
for Barry Cortez, Chief  
Pesticide Registration Branch  
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\_\_\_\_\_  
May 16, 1997

Date

Enclosures

cc: Ms. Ann Prichard

RISK ASSESSMENT OF TALSTAR® T&O

BIFENTHRIN RISK CHARACTERIZATION DOCUMENT B:

SUBSEQUENT TO

BIFENTHRIN (CAPTURE 2 EC) RISK CHARACTERIZATION DOCUMENT, 1991

HEALTH ASSESSMENT SECTION  
MEDICAL TOXICOLOGY BRANCH  
DEPARTMENT OF PESTICIDE REGULATION  
CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

February 10, 1997

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## TECHNICAL SUMMARY

This document contains a risk assessment of Talstar® T&O WSB and Talstar® T&O Flowable for use on greenhouse ornamental trees, shrubs, plants, flowers, and non-bearing fruit and nut trees. Bifenthrin is the active ingredient in Talstar® T&O. A risk characterization document (RCD) on bifenthrin for the full registration of Capture® 2 EC-Cal on cotton was completed in 1991 (Reed, 1991). It contains a comprehensive toxicological database of bifenthrin. This Talstar® T&O risk assessment is a second part (Part B) to the 1991 RCD. It provides an update on the toxicological database and includes only information pertinent to the assessment of Talstar® T&O use.

### HAZARD IDENTIFICATION AND DOSE-RESPONSE ASSESSMENT

The oral median lethal dose ( $LD_{50}$ ) for Talstar® T&O is 695 mg/kg in rats. The dermal  $LD_{50}$  is above 2,000 mg/kg in rabbits. The inhalation median lethal concentration ( $LC_{50}$ ) is 1.89 mg/l (4-hr whole body exposures) in rats. Talstar® T&O WSB caused no eye irritation and mild to slight dermal irritation (category IV irritant).

In the 1991 RCD, an oral no-observed-effect level (NOEL) of 1 mg/kg/day was used to characterize the acute exposures of workers. For occupational exposures that were mostly dermal, using a dermal instead of an oral NOEL to calculate the margin of exposure (MOE) would avoid the uncertainties inherent in the cross-route extrapolation. The selection of a critical NOEL for greenhouse workers was re-evaluated at the request of the registrant, although no pertinent new data has been submitted since 1991. The re-evaluation focused on the oral and dermal toxicological databases and the accompanying uncertainties for their use in risk assessment. The oral toxicity database was more extensive and showed a good consistency among studies. The bolus dosing using corn oil as vehicle did not appear to substantially increase the oral toxicity of bifenthrin. The dermal toxicity database showed less consistency in clinical observations and had substantial uncertainties regarding the study conduct. Uncertainties in the risk assessment also existed when the dermal dose was expressed on a per body weight instead of per surface area basis. A difference in absorption rates would be expected between the treatment in animals (large amount over a small area) and the occupational exposures (small amount over a larger area). However, no data on pharmacokinetics were available for assessing the difference. It was concluded that the oral NOEL of 1 mg/kg/day used in the 1991 RCD should continue to be used in the risk assessment for Talstar®.

A report on the re-reading of the histopathological slides from the oncogenicity study in mice was submitted after the completion of the 1991 RCD. It was reviewed for its implication to the risk assessment of Talstar®. Based on the report, DPR concluded that the urinary bladder tumors should be classified as urinary bladder sarcoma - NOS, rather than leiomyosarcoma as originally reported. However, the peer-review process in the re-reading of slides was not sufficient to support a revision of the tumor incidences. The report speculated that the tumors were not likely to be malignant and may not be relevant to humans. However, the concern for tumors remained because of the higher number of invasive tumors and masses in the higher dose groups. It was concluded that the quantitative approach to risk assessment for oncogenic effects used in the 1991 RCD should continue to be used.



## EXPOSURE ASSESSMENT

The exposures of workers associated with the greenhouse use of Talstar® T&O were assessed. Both the occupational exposure and the total exposure were presented. The total exposure was the sum of the occupational and dietary exposures. Dietary exposures were anticipated based on the registered use of Capture® 2 EC on cotton and the emergency use on various vegetable crops and cucurbits since 1991. A dermal absorption factor of 17.9% was used to calculate the absorbed dose from occupational exposures. Because the critical NOEL and the oncogenicity potency were based on oral studies, the occupational dose was subsequently converted to an oral equivalent exposure by an oral absorption factor of 28% determined in the 1991 RCD.

The respective acute absorbed daily doses from occupational exposures were 1.1-1.4, 61.0-156.3, and 129.8-173.0  $\mu\text{g/kg/day}$  for mixer/loaders, applicators, and harvesters of greenhouse flowers. The respective acute oral-equivalent total exposures for the three work tasks were 6.1-7.2, 220.1-560.4, and 465.8-620.1  $\mu\text{g/kg/day}$ . The respective lifetime average absorbed dose for the three work tasks were 0.01, 0.2-2.7, and 7.1-9.5  $\mu\text{g/kg/day}$ . The respective oral-equivalent total exposures for the three work tasks were 0.039, 0.717-9.646, and 25.360-33.932  $\mu\text{g/kg/day}$ .

## RISK CHARACTERIZATION

The risk of acute exposures was characterized by the margin of exposure (MOE). The MOE is the ratio of the NOEL over the exposure. The risk from chronic, long-term exposures was characterized quantitatively by multiplying the potency by the lifetime average daily exposure.

Based on the oral NOEL of 1.0 mg/kg/day (tremors in rats), the MOEs for the mixer and loader were 140-160. A MOE of at least 100 is generally considered protective of human health when the adverse effect is based on animal data. The MOEs for applicators and harvesters were 5 to 2. For these workers, dietary exposures contributed less than 1% to the total exposure and was considered insignificant.

The oncogenic risk for mixers and loaders were the lowest, with the lifetime probability of oncogenic effects ranging from 1 to  $2 \times 10^{-6}$ . The risk of applicators ranged from  $2-3 \times 10^{-5}$  to  $3-4 \times 10^{-4}$ . The risk was highest for the harvesters, ranging from  $7-11 \times 10^{-4}$ . Dietary exposures contributed less than 1% to the total lifetime exposures for all workers.

## RISK APPRAISAL

A qualitative presentation of uncertainties in the determination of the critical NOEL was presented under Hazard Identification and Dose-Response Assessment. Uncertainties exist when an oral NOEL is used to calculate the MOE for dermal exposures. Adjusting for the route-specific absorption factor and the apparent species sensitivity between the two test species, the difference between the critical NOEL for oral and dermal routes could be approximately 2- to 4-fold. Therefore, the MOE could theoretically be scaled up to 4 - 20 for harvesters and applicators. Uncertainties in the exposure assessment and the oncogenicity data that formed the basis of risk estimates are also presented. The risk of local dermal effects was not assessed due to insufficient information on the exposure.

## RISK ASSESSMENT FOR TALSTAR® T&O

### I. BACKGROUND

This document contains a risk assessment of the greenhouse, non-food use of Talstar® T&O WSB and Talstar® T&O Flowable. Talstar® T&O Flowable was registered in California in May, 1995. However, a risk assessment has not been conducted for its use. Talstar® T&O WSB contains 9.9% bifenthrin and Talstar® T&O Flowable contains 7.9% bifenthrin. These formulations are for use on greenhouse ornamental trees, shrubs, plants, flowers, and non-bearing fruit and nut trees. The labels specify a maximum Talstar® T&O application rate of 0.2 lb/100 gallons of water. However, the labels do not specify the maximum amount of spray solution per area or the maximum number of applications.

A risk characterization document (RCD) on bifenthrin, specifically for the Section 3 registration of Capture® 2 EC-Cal for cotton, was completed in 1991 (Reed, 1991). The database on the physical and chemical properties, the environmental fate, and the toxicity profile of bifenthrin were presented in the 1991 RCD.

Since 1991, Capture® 2 EC-Cal has also been used on many food crops in California under Section 18 (Emergency Exemption) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Acute dietary exposures from bifenthrin residues in Section 18 commodities and in cotton and/or its products are included in the assessment of the total exposures of greenhouse workers to bifenthrin.

### II. HAZARD IDENTIFICATION AND DOSE-RESPONSE ASSESSMENT

A detailed toxicological profile of bifenthrin was given in the RCD for Capture® 2 EC-Cal (Reed, 1991). This section presents the toxicological data that have been submitted since 1991. They include: 1) the acute toxicity of Talstar® 80 G/L Flowable and 2) the reports on the re-evaluation of histopathological slides from the mice oncogenicity study. The data for the acute toxicity of the formulation did not directly impact the selection of the critical acute no-observed-effect-level (NOEL) previously used in the 1991 RCD for characterizing the acute exposures. The results of the pathological re-evaluation of slides also did not provide sufficient basis for deviating from the dose-response relationship defined for oncogenicity in the 1991 RCD. Although no new data pertaining to the selection of a critical acute NOEL have been submitted, the relevant toxicological data for determining a critical NOEL for acute exposures of greenhouse workers were re-evaluated at the request of the registrant (FMC, 1995). The issues considered in the re-evaluation are presented in this section.

#### II.A. Acute Toxicity of Talstar® Formulation

Based on the acute oral, dermal, and inhalation toxicity studies for FMC 54800 (Talstar®) 80 G/L Flowable submitted to DPR, the oral median lethal dose (LD<sub>50</sub>) for the formulation was 695 mg/kg in rats (DeProspo, 1984a), the dermal LD<sub>50</sub> was above 2,000 mg/kg in rabbits (DeProspo, 1984b), and the inhalation median lethal concentration (LC<sub>50</sub>) was 1.89 mg/l (4-hr whole body exposures) in rats (DeProspo, 1988). Based on studies on eye irritation (DeProspo, 1989) and skin irritation (DeProspo, 1984c), Talstar® T&O WSB was determined to be a category IV eye and dermal irritant.

Data on dermal sensitization potential of bifenthrin formulations are presented in the exposure assessment document (Dong, 1996). Capture® 2 EC was determined to be a dermal sensitizer based on a study in guinea pigs (DeProspo, 1983). In another study by DeProspo (1984d), however, no sensitization was reported for Talstar® T&O. The current labels for Talstar® products do not include a statement on dermal sensitization potential (Dong, 1996).

## II.B. The Critical NOELs for Acute Exposures

In the 1991 RCD, an oral NOEL of 1 mg/kg/day was used to characterize the risk of acute exposures both from dietary exposures (the general population) and the exposures of workers associated with its use on cotton. In 1995, the registrant proposed the use of a dermal NOEL in characterizing the risks of greenhouse workers' exposures, since the exposures of greenhouse workers are mainly dermal (FMC, 1995).

Whenever possible, a route-specific NOEL should be used in characterizing the risk of an exposure through the same route. For workers' exposures that are mostly dermal, the use of a dermal NOEL for risk characterization would avoid the uncertainties inherent in the cross-route extrapolations. However, substantial uncertainties exist in the current dermal toxicity database for establishing a definitive NOEL for acute exposures. The considerations for determining a critical NOEL are presented.

### II.B.1 Oral NOELs in Rats

Signs of neurological toxicity have been noted in the acute toxicity studies for determining the LD<sub>50</sub> for either technical bifenthrin or its formulations. A single oral dose of 20 mg/kg technical grade (91.4% purity) bifenthrin, or 18.3 mg/kg bifenthrin, resulted in tremors in 6 of the 10 rats, as early as 3 hours after dosing (Freeman, 1982). Tremors, chromorrhinorrhea, clonic convulsions and death occurred in rats that were treated with 150 mg/kg FMC 54800 2 EC which contained 26.5% bifenthrin, or 39.8 mg/kg bifenthrin. The same neurotoxicity signs were observed with a single oral dosing of 500 mg/kg Talstar® 80 G/L Flowable which contained 8% bifenthrin, or 40 mg/kg bifenthrin.

The current database on clinical observations shows consistency in the NOEL determined from oral gavage and feeding studies. A NOEL of 1 mg/kg/day was established from a teratology study through oral gavage. The NOEL was based on tremors observed in 18 of 25 pregnant rats (starting day 4 of exposure) at the next higher dose of 2.0 mg/kg/day (DeProspo, 1984e). An acute NOEL can also be determined from two feeding studies: a chronic toxicity study by McCarty (1986) and a 90-day toxicity study by Rand (1984). In both of these studies, tremors were observed in rats starting on day 3 of consuming diets that contained 100 ppm bifenthrin (5 mg/kg/day) and starting on day 2 at 200 ppm bifenthrin (10 mg/kg/day). Based on tremors, the acute NOEL from these two studies was 50 ppm in the diet (2.5 mg/kg/day). The NOELs from these three studies differed by 2.5-fold. The lowest NOEL of 1 mg/kg/day was used in 1991 to characterize the risk of acute exposures (Reed, 1991).

A concern was raised regarding the validity of using a NOEL determined from an oral gavage study using corn oil vehicle (FMC, 1995). The two specific underlying issues were the dosing method (i.e., bolus) and the possible enhancement of toxicity by corn oil. While these two factors may affect the toxicity of a chemical, the extent of the effects would understandably be dependent to chemicals in general, the conditions under which exposures occur, and the specific toxicity under evaluation. For a chemical such as bifenthrin that has very low water solubility (<0.1 ppb) and having a physical appearance of viscous oil that hardens to a solid (Reed, 1991), the use of a delivering vehicle is necessary. A study by Crofton *et al* (1995) was submitted as an evidence of a marked enhancement of toxicity by corn oil. Crofton *et al* (1995) studied the effects of 4 vehicles (i.e., corn oil, Emulphor, glycerol formal, methylcellulose) on the toxicity of deltamethrin in rats. The results showed that the ED<sub>50</sub> (effective dose of 50% response) for motor activities was nearly two orders of magnitude lower with corn oil and glycerol formal than with methylcellulose. However, as the authors also pointed out, there was no accompanying pharmacokinetic data to identify any relationship that may contribute to the apparent differences in toxicity. It should be noted that the mode of chemical delivery was very different for the four tested vehicles (i.e., solubilizing versus suspending). These differences may significantly affect the availability of deltamethrin in the gastrointestinal tract. Without further investigation, the results of the study with deltamethrin toxicity cannot be directly used to dismiss the pertinence of corn oil gavage regimen in bifenthrin risk assessment.

When evaluating the risk of a chemical, it is preferable to rely on the database that is specific for the chemical under evaluation rather than to extrapolate from other databases. Contrary to the report on deltamethrin by Crofton *et al* (1995), the available database on bifenthrin showed that bolus dosing in corn oil did not cause a substantial enhancement of toxicity when compared to other oral dosing regimens (e.g., dietary inclusion). This was illustrated in a comparison presented earlier in this section regarding the NOEL and/ or LOEL (lowest-observed-effect level) from different oral dosing regimens. The acute NOELs and LOELs from the teratology study (bolus dosing with corn oil vehicle) by DeProspo (1984e) and the dietary inclusion studies (dietary inclusion using acetone vehicle in diet preparation) by Rand (1984) and McCarty (1986) showed a possible difference of only 2.5 fold in bifenthrin toxicity. Thus, the database on bifenthrin supports the use of a NOEL determined in a gavage study using a corn oil vehicle. In as much as evaluating the risk to human health is the primary concern, studies using corn oil vehicle are relevant because corn oil is a common component in human diets.

#### II.B.2. Dermal NOELs in rabbits

Neurological signs of toxicity similar to those observed in oral studies were also noted in rabbits after dermal exposures to bifenthrin and its formulation products. Currently on file in DPR are three acute studies from which the LD<sub>50</sub> of the technical grades and formulations were determined. In these studies, a single dose of 2,000 mg/kg of either technical grade or the formulations of bifenthrin was used. No clinical effects were reported in the study with technical grade FMC 54800 (Freeman, 1983a). No toxicity was reported in the study with technical grade bifenthrin. Neurologic effects were reported in rabbits treated with formulations (2 EC or 80 G/L Flowable). It was interesting to note that signs of toxicity were observed both within a day after dosing and also several days after dosing and persisted throughout the end of the 14 day observation period. For example, after the single application of the two formulations, tremors were reported on day 1 of exposure, and persistent lacrimation and nasal discharge were not noted until day 6 of 2 EC treatment (Freeman, 1983b) or day 10 of 80 G/L treatment (DeProspo, 1984f). The amount of bifenthrin at the administered level, calculated based on the amount of bifenthrin in the formulations, were 530 and 160 mg/kg, respectively, for 2 EC and 80 G/L

Flowable. Assuming that these levels were the LOELs, and using the default uncertainty factor of 10 to extrapolate from the LOEL to NOEL (Dourson and Stara, 1983), the estimated NOEL could be as low as 16 mg/kg. This was far lower than the 2,000 mg/kg technical grade bifenthrin at which no effects were noted. The apparent differences in sensitivity to the technical grade and formulations could be due to the inert ingredients and/or adjuvants in the formulations. This consideration was pertinent for risk assessment because some workers (e.g., mixers and loaders) could realistically be exposed to the formulations rather than the technical grade bifenthrin. On the other hand, the differences could also be due to a lack of emphasis in these LD<sub>50</sub> studies on noting effects other than lethality. This speculation was based on the observation that, although no toxicity was reported at 2,000 mg/kg in the acute toxicity study by Freeman (1983a), the loss of muscle coordination was noted on day 2 of exposure at a much lower dose (i.e., 500 mg/kg) in a 21-day study by DeProspero (1984g). The uncertainty in determining a critical NOEL for risk assessment from LD<sub>50</sub> type studies was also demonstrated in the oral toxicity database. While the acute NOELs from the LD<sub>50</sub> studies ranged from 18.3 to 40 mg/kg (Section II.B.1) the acute NOEL established within 2-3 days of dosing from teratology, subchronic, chronic studies were much lower. In the latter studies, the NOELs ranged from 1 to 2.5 mg/kg.

An apparent acute dermal NOEL could also be established from the 21-day dermal toxicity study by DeProspero (1984g). In this study, 6 rabbits per gender were treated with bifenthrin at 25, 50, 100, or 500 mg/kg for 21 days. Technical grade bifenthrin (88.35% purity) was applied daily to a 4x4 inch gauze on the shaved back and wrapped with plastic coverings for 6 hours. At the end of each exposure period, the gauze and wrap was removed and the surface wiped first with gauzes wetted with acetone, then with water. An everted collar was fitted to the animals throughout the study period. At 500 mg/kg, loss of muscle coordination was noted in 11 of the 12 males and females as early as on day 2 of treatment, while tremors were not reported until day 9 (3 of 6 males) or day 19 (2 of 6 females). At 100 mg/kg, lacrimation was observed in one female starting on day 10 and tremors were reported in another female on day 17. The lack of annotation of tremors during the earlier part of this 21-day study is puzzling. In the dermal LD<sub>50</sub> studies, tremors were noted earlier (day 1) than other effects (i.e., nasal discharge starting day 6 or 10).

Another area of concern was that the loss of a collar was reported as the cause for the only case of death (a female at 500 mg/kg) and the only case of tremors on day 17 (a female at 100 mg/kg). The lack of reporting on the frequency with which animals lost their collars during the study was a concern. The toxicological significance of the loss of collar was also unclear. In these cases, a question remained as to how much residual bifenthrin could be ingested through either the plastic wrap or on the skin after washing with acetone and water. These uncertainties in the quality of the study reduced the confidence for using this study in establishing a definitive NOEL for risk assessment. Without a definitive reason for discounting the tremors observed at 100 mg/kg, the NOEL based on tremors was 50 mg/kg. This NOEL could be used to assess an acute exposure because the effects at the LOEL of 100 mg/kg could potentially be a result of a single or a few exposures. This was supported by the delayed appearance of neurological signs of toxicity in the dermal LD<sub>50</sub> studies. As noted earlier in this section, lacrimation or nasal discharge started 6 or 10 days after a single treatment and persisted till the end of the 14-day observation period.

In addition to tremors and the lack of muscle coordination, lacrimation was also noted in the treated rabbits in the 21-day study. Lacrimation appeared to be a common sign of toxicity among a battery of neurological manifestations reported either prior to or after the observation of

tremors. Among the 6 animals in each treatment group, lacrimation was reported in one female at 50 and 100 mg/kg on day 13 and 10, respectively, and the effect persisted till the end of the 21-day study period. The NOEL based on lacrimation was 25 mg/kg.

Depending on the neurological endpoints (i.e., tremors and/or lacrimation), the dermal NOEL determined from the 21-day study could be 25 or 50 mg/kg. Adjusting for the route-specific absorption factors (28% and 17.8% respectively for oral and dermal routes), and excluding the consideration of species sensitivity, these NOELs determined in rabbits were 16- to 32-fold higher than the oral NOEL in rats. Pertinent pharmacokinetic data would be useful for reconciling the differences in toxicity between the two routes and two species. However, data on blood concentration profiles from dermal exposure were unavailable for a comparison with the existing oral pharmacokinetic profile.

Aside from the specific uncertainties in the bifenthrin dermal toxicity database that preclude the use of a dermal NOEL for the evaluation of risk, it is also important to note that there are several general areas of uncertainty when a dermal NOEL determined in laboratory animals is used to assess the risk of human exposures. One inherent issue is the potential difference in amount of absorption between animals and humans. The skin of laboratory animals is generally more permeable than human skin. The absorption is dependent on anatomical and physiochemical factors that are specific not only for a chemical but also for the exposure conditions. Without data for these factors, an appropriate interspecies adjustment cannot be made. Another issue is the difference in the contact surface area between the animal experiments and human exposure scenarios. In animal studies, test substances are applied to the shaved back of laboratory animals (in this case, rabbits) in an area less than 10% of the total body surface area. Whereas, depending on the exposure scenarios, human exposures could involve a greater percentage of the total body surface area. Unfortunately, the general relationship of increased absorption with increasing surface area cannot be reflected in the dose per unit body weight commonly used for dermal toxicity studies. Another area of uncertainty is the dependence of absorption on the concentration at the site of contact. The percentage of skin absorption generally decreases with the increasing concentration at the site of contact (Chang and Riviere, 1991). Unfortunately, no pharmacokinetic data are available for adjusting the absorption factor between the high concentration over a smaller surface area in animal studies and the lower concentration over a larger surface area which may commonly characterize the human exposures.

#### II.B.3. Species sensitivity

In addition to the aforementioned considerations (i.e., route of exposures, the endpoints of toxicity, and the quality of studies), species sensitivity should also be considered in the selection a critical NOEL for risk assessment. In general, the critical NOEL should be determined from the most sensitive species tested. A comparison between the two available teratology studies in rats (DeProspo, 1984e) and in rabbits (DeProspo, 1984h) showed that pregnant rats were apparently more sensitive than pregnant rabbits. The interspecies comparison was possible because these two studies followed comparable study protocols. While no effects were noted in rabbits at 2.67 mg/kg, tremors occurred in rats at 2 mg/kg. Based on the difference in the NOELs and LOELs of the two studies, rats could be 2- to 3-fold more sensitive than rabbits.

#### II.B.4. Critical NOEL for systemic effects

The review of the toxicological database concluded that the same NOEL of 1 mg/kg used in the 1991 RCD remains valid for assessing the exposures of workers associated with the greenhouse

use of Talstar® T&O Flowable. The NOEL was also used by USEPA in characterizing the risk of occupational exposures (USEPA, 1995). In the Exposure Assessment (Dong, 1996), the occupational exposures that were considered to occur primarily through the dermal route and were expressed in terms of the absorbed dose per body weight. Since the critical NOEL was based on oral studies, it is necessary to convert the absorbed dermal dose to an oral equivalent exposure for the calculation of the margins of exposure (MOE) and risk. The oral equivalent exposure was calculated as the dermal absorbed dose divided by the oral absorption factor of 28%, the same factor used in the 1991 RCD.

#### II.B.5. Critical NOEL for local effects

In addition to neurological effects, rabbits in the 21-day dermal toxicity study by DeProspero (1984g) also showed erythema at all dose levels. Of the 11-12 male and female animals per dose group, 2 - 9 had erythema beginning as early as day 2 of treatment. By applying a default uncertainty factor of 10 to the lowest tested level of 25 mg/kg, the estimated NOEL would be 2.5 mg/kg. Dermal effects were also reported in humans. Among the 5 cases of workers' illnesses recorded from 1990-93 that could be attributed to exposures to bifenthrin, two cases involved itching, skin irritation, and rash.

The focus of the 1991 RCD was on the systemic effects and did not evaluate the potential for localized dermal effects. The risk of localized effects on the skin should also be characterized whenever human exposures based on the contact surface area can be estimated.

#### II.C. Oncogenicity

In the 1991 RCD, the risk from potential long-term exposures was characterized based on oncogenic effects. In a chronic toxicity study in mice (Geiger, 1986), urinary bladder tumors and hepatocellular tumors were reported in the males, and lung tumors were reported in the females. A detailed discussion on the weight of evidence considerations and the tumor incidences were presented in the 1991 RCD. Based on the evidence of multiple tumors in mice, USEPA classified bifenthrin as a C<sub>q</sub> carcinogen, a possible human carcinogen according to the agency's 1986 carcinogen risk assessment guidelines, and recommended a quantitative approach to risk assessment. USEPA has not reassessed the oncogenicity risk based on the agency's proposed carcinogen risk assessment published on April 23, 1996 (USEPA, 1996).

Since the completion of the 1991 RCD, the registrant initiated a re-evaluation of the histopathological slides for the oncogenicity study in mice (Butler, 1991). Based on the results of these evaluations, the Carcinogenicity Peer Review Committee (PRC) of the Health Effect Division within the USEPA Office of Pesticides Program re-evaluated the oncogenicity database of bifenthrin in 1992. The PRC concluded that bifenthrin should remain as a C carcinogen, however, not as a C<sub>q</sub> carcinogen. The PRC recommended that the risk of long-term exposures should be evaluated based on non-oncogenic endpoints, instead of taking a quantitative approach to risk assessment based on oncogenic endpoints (USEPA, 1992). The current RfD of 0.015 mg/kg/day was established from the NOEL of 1.5 mg/kg/day determined in the dog study by Serota (1985) based on tremors. It is important to note that this chronic NOEL is higher than the acute NOEL of 1 mg/kg/day established in rats.

In 1994, DPR requested and reviewed the reports on the histopathological re-evaluations. DPR concluded that they: 1) provided sufficient evidence for changing the type of tumors from leiomyosarcoma to urinary bladder sarcoma, NOS, 2) did not provide sufficient information

for revising the overall incidence of urinary bladder tumors and 3) did not provide convincing arguments that the tumors found in mice were not relevant to humans. The discussions of these issues are presented below.

#### II.C.1. The re-evaluation of pathological slides

The histopathological slides from the oncogenicity study in mice (Geiger, 1986) were re-evaluated in 1991 by a panel of three pathologists (Butler, 1991). Slides of urinary bladder, liver, and lung from all treatment groups were initially reviewed by Dr. Butler. The results of the re-evaluations of liver and lung tissues were unremarkable. Slides of urinary bladder that were identified as having a submucosal tumor or focal spindle proliferation by Dr. Butler were then reviewed by Drs. S. M. Cohen and R. A. Squire. The pathologists considered the neoplasms, originally classified as leiomyosarcoma, were "submucosal tumors", "sarcoma" or "focal proliferative lesions". The partial re-evaluation (i.e., all slides were not reviewed by all three pathologists) resulted in a substantial change in the tumor incidences and the pattern of dose-response relationship from the original report. The report also stated that the morphological type of these tumors had not been found in human urinary bladders.

In 1994, USEPA established a set of criteria for accepting any voluntary submission of pathological re-reads (USEPA, 1994). The need for a policy stemmed from the increasing number of requests for USEPA to reconsider the Agency's decisions based on re-evaluation of pathological findings. USEPA requires the use of a peer-review procedure similar to the Pathology Working Group (PWG) used by the National Toxicology Program (NTP) to resolve differences in diagnosis between the peer-review pathologist and the study pathologist. The PWG, consisting of the study pathologist, the peer-review pathologist, and other pathologist(s), examines the tissues without any knowledge of treatments or prior diagnoses. For a voluntary submission of a revised pathology diagnosis, USEPA requires that all target tissue slides from all dose groups be re-read by the peer-review pathologist and, as a minimum, all slides with significantly different diagnosis should be reviewed by the other peer reviewers. It appeared that the minimum requirement of having positive slides examined by the other two pathologists might have been met in this case. However, there was no indication whether the reviewers were given the information on treatments or prior diagnoses. The conduct and extent of the peer-review are important issues especially when this study is a major source for oncogenicity evidence and that the re-evaluation became the basis on which to petition for dismissing the initial evaluation. The specific concern about the change of tumor incidences will be discussed in greater detail in a subsequent section (II.C.3).

#### II.C.2. The classification of the urinary bladder tumors

The re-evaluation report showed a general agreement among the three pathologists regarding the histopathology of male mice urinary bladder tumors. The tumors were termed "submucosal tumor" or "submucosal sarcoma". Therefore, it was more appropriate to classify these tumors as "urinary bladder sarcoma, NOS", not "urinary bladder leiomyosarcoma" as originally classified. Alternately, based on the same re-evaluation report, USEPA PRC concluded that these tumors were "hemangiopericytoma". However, this terminology was not used by any of the three pathologists who re-evaluated the slides. The tumors were reported as having an unknown pathogenesis and some were noted as showing invasion at the termination of the study (18 months).



### II.C.3. The incidence of the urinary bladder tumors

The re-evaluation resulted in a change in the tumor incidences in male mice. The re-evaluation uncovered 5 additional tumor-bearing animals in the control group. The increase in tumor incidence in the controls not only affected the overall outcome of a statistical analysis of the dataset but also suggested that a lower level of statistical criterium (i.e.,  $p$  at 0.01) should be used. It should be noted, however, that the overall tumor incidences for the controls and all treatment groups were not peer reviewed by all three pathologists. All the slides from all treatment groups were re-evaluated by only one pathologist (Butler) while the other two pathologists (Cohen and Squire) reviewed only the selected slides that Dr. Butler considered as positive. Consequently, the significance of the revised tumor incidences is uncertain. To answer the question about the incidence would require that the entire peer review group views all slides of the target organ (McConnell and Eustis, 1994). This is an important issue especially when the incidence in the controls was raised substantially (from 2 to 6 or 7 per 47 or 48 control male mice) while the incidence of all other treatment groups (50, 200, 500, and 600 ppm in the diet) remained similar to the original readings (i.e., plus/minus 1). Similar concern was also raised by the USEPA PRC (USEPA, 1992) that reviewed the re-evaluation report by Butler (1991).

### II.C.4. Relevance of bladder tumors to humans.

Butler (1991) considered these tumors not relevant to humans because they have been reported mainly in mice and not in humans. The consideration by the HED PRC that resulted in the change of the carcinogen classification from  $C_q$  to C was mainly based on the change of tumor classification from the highly malignant leiomyosarcoma to hemangiopericytoma, a tumor "not likely to be malignant" and "may not be uncommon in this strain (of mice)" (USEPA, 1992). It should be noted, however, that there was a dose-related increase in tumors classified as invasive. While there were no invasive tumors in the control group, approximately 50% of the tumors at the high dose group were noted as invasive. Also, mice in the two highest dose groups had an associated urinary bladder mass (1 mouse at 500 ppm and 2 mice at 600 ppm) while no mice from the lower dose or control groups had a mass. The increase in invasive tumors and the mass remained of concern. It is possible that tumors in the higher dose groups were initiated earlier or were progressing at a faster rate.

The current understanding of the implication of animal oncogenicity studies is that they are designed for identifying the potential of test substances to cause oncogenic effects in humans and not necessarily for identifying the specific potential site or target organ in humans (NRC, 1994, USEPA, 1996). Historically, site concordance among laboratory animals and between animals and humans has not been consistently demonstrated. The predictive nature of the animal studies is that if a substance causes tumors in animals, it has the potential to also cause tumors in humans. The weight of oncogenicity evidence of a positive bioassay outcome could be lessened if a type of tumor occurs exclusively in animals through a demonstrated mechanism known to be impertinent to humans. Stating that a type of tumor has not been seen in humans based on histopathological examinations alone would not, by itself, be sufficient for dismissing the potential for oncogenic effects in humans. In the case of bifenthrin, not only was the mechanistic data not available, the three pathologists who conducted the re-evaluation were also not able to accurately define the histogenesis of the tumors (Butler, 1991). Regarding the weight of evidence, it should also be noted that the mice study also showed some evidence of oncogenicity in the liver and lung (Reed, 1991).

Based on the above considerations, the reports submitted on the re-evaluation of slides were not sufficient to justify for a change in either the weight of evidence consideration or the quantitative

approach to the bifenthrin oncogenicity risk assessment as presented in the 1991 RCD. Although the additional number of tumor-bearing animals in the control group was confirmed in the re-evaluation, the incidences of urinary bladder tumors in the treatment groups were not re-evaluated by two of the three pathologists and thus considered not verified. Without a verification of the tumor incidence in all dose groups, DPR has no data on which to base any change in the potency that was previously determined for bifenthrin. Consequently, the lifetime oncogenic risk was estimated based on the maximum likelihood estimate (MLE) of potency of  $2.6 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$  and its 95% upper confidence bound (UB) of  $4.3 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$ , the same potency values used in the 1991 RCD. This approach does not reflect a reassessment based on the recently published USEPA proposed carcinogen risk assessment guidelines.

### III. EXPOSURE ASSESSMENT

Workers exposed to bifenthrin as a result of the greenhouse use of Talstar® T&O include those who mix, load, and apply Talstar® T&O and those who harvest and/or handle plant materials that have been treated with Talstar® T&O. The greenhouse use by itself is not expected to result in dietary exposures of bifenthrin. However, Capture® 2 EC-Cal, another formulation that contains bifenthrin, is currently permitted for use on cotton under a Section 3 Full Registration. In addition, Capture® 2 EC-Cal had also been used for several years under the FIFRA Section 18 Emergency Exemption on various crops in California. Therefore, the total acute exposure of a worker consists of 1) dietary exposures through the use of Capture® 2 EC-Cal on agricultural commodities and, 2) occupational exposures from the greenhouse use of Talstar® T&O. The crops under the Section 18 uses were not included in the dietary exposure components of the chronic risk assessment for the Talstar registration. The exposures should be evaluated when they are under consideration for Section 3 registrations or when they are reconsidered for Section 18 uses subsequent to the 1996 use permits. The estimation of dietary exposures and a brief description of the occupational exposures conducted by Dong (1996) are presented in this section.

#### III.A. Dietary Exposures

The use of Capture® 2 EC-Cal on cotton could potentially result in residues not only in cotton products (i.e., oil and meal) but also secondary residues in animal products (e.g., meat, milk, and their by products) due to the inclusion of cotton by-products in the feed. Dietary exposures could also result from the use of Capture® 2 EC-Cal on vegetable crops and cucurbits under Emergency Exemptions. These vegetable and cucurbit commodities include: broccoli, cauliflower, cabbages, rapini, lettuce, melons, cucumbers, squash, pumpkins. They are included in the estimation of acute dietary exposures.

##### III.A.1. Residue data

No monitoring data for bifenthrin residues on cotton, vegetable crops, and cucurbits were available. The anticipated residue levels calculated from field trials for cotton and the action levels for Section 18 registered crops were used. A list of the residue level used in the acute and chronic dietary exposure assessment is given in Table 1.

##### Acute exposures

In the 1991 RCD, the maximum anticipated residue level for cottonseed oil and meal (0.085 ppm) was estimated from a total of 16 field trials. Residue levels in meat and milk were subsequently

Table 1. Residue concentration in commodities and food forms used in the dietary exposure assessment<sup>a</sup>.

Foods and Food forms	Acute Exposures	Chronic Exposures
Melons (Cantaloupes, Casaba, Crenshaw, Honey-dew, Persian melon, Winter melon, watermelon)	0.1	-
Cucumbers, Squash (winter & summer), towelgourd	0.2	-
Pumpkin	0.1	-
Broccoli	0.1	-
Cabbage-green & red, Chinese, bok choy	2.0	-
Cauliflower	0.05	-
Lettuce - leafy, unspecified	0.6	-
Lettuce - head	0.05	-
Cottonseed-oil, meal	0.085	0.022
Milk	0.0012	0.0003
Beef, Sheep, Goat - meat byproducts, organ, other	0.0085	0.0022
- boneless, fat	0.017	0.0044
- kidney	0.001	0.00026
- liver	0.0002	0.000053
- boneless, lean	0.00092	0.00024
Beef -dried	0.0018	0.00046
Pork - meat byproducts, organ, other	0.0028	0.00073
- boneless, fat	0.0057	0.0015
- kidney	0.00034	0.000088
- liver	0.000068	0.000018
- boneless, lean	0.00031	0.000079

<sup>a</sup>/ Residues for a) cucurbits (melons, cucumbers, squash, pumpkin) were the action levels for FIFRA Section 18 (Emergency Exemption) use; b) cottonseed products were estimated from field trials. The highest and the average levels were used for acute and chronic exposures, respectively; c) beef, sheep, goat, pork and their products were estimated based on feed contributions of cotton products and feed-to-animal transfer factors experimentally derived.

estimated based on default transfer factors from the feed. A detailed description of the supporting database and calculations were presented in the 1991 RCD (Reed, 1991). Since no monitoring data were available, the same residue levels used in 1991 were also used in the present analysis. Residue levels for commodities listed under the Section 18 use were assumed to be at the action levels established for the use. These action levels were: 2.0 ppm in cabbage, 0.1 ppm in broccoli, 0.05 ppm in cauliflower, 2.0 ppm for lettuces with wrapper leaves or 0.05 ppm without wrapper leaves, and 0.2 ppm for whole cucurbits or 0.1 ppm for the pulp.

#### Chronic exposures

Since cotton is the only commodity listed in the Full Registration for bifenthrin products, only cotton products and the secondary residue in meat and milk products were included in the assessment. The average anticipated residue level of 0.022 ppm for cottonseed oil and meal used in the 1991 RCD was also used in this analysis.

#### III.A.2. Dietary exposure levels

Dietary exposures were estimated as a product of the residue level multiplied by the consumption rate. A detailed description of the estimation of exposure is presented below. The estimated exposure levels are summarized in Table 2.

#### Acute exposures

An acute dietary exposure analysis was conducted using the Exposure-4™ software program developed by Technical Assessment Systems, Inc. (TAS). The Exposure-4™ program estimates the distribution of user-day (consumer-day) exposure for the overall U.S. population and specific population subgroups (TAS, 1996a). A user-day is any day in the survey in which at least one food from the specific commodity list is consumed. The consumption analysis used individual food consumption data from the U.S. Department of Agriculture (USDA) Continuing Survey of Food Intakes by Individuals (CSFII), combining the 3-year survey data from 1989-90, 1990-91, and 1991-92 (USDA, 1989-91).

The dietary assessment was conducted for all commodities that included cotton and the FIFRA Section 18 commodities (Set 1, "with cotton") or excluding cotton (Set 2, "no cotton"). The exposures given in Table 2 represented the 95th percentile of the user-days exposures. The 95th percentile exposure from Set 2 was usually higher than Set 1 (i.e., except for nursing infants less 1 year old) due to a change in the size of the user-day population. The total number of user-days for Set 1 was much larger because it included days that meat and milk was consumed. The overall lower exposures from meat and milk (mostly due to lower residue levels in these commodities) than from the specific vegetable and cucurbits caused a shift of the exposure distribution to the left, resulting in a higher frequency of distribution at the lower exposure levels. This can be illustrated with the exposure profiles for the US population. The respective total number of user-days for Set 1 was 35,433, representing a greater than a 2-fold increase in user-days than for Set 2 (16,610 user-days). The frequency distribution of both sets of exposures are presented in Figure 1. The expanded region in Figure 1 shows the respective exposures of 1.1 and 2.2  $\mu\text{g}/\text{kg}/\text{day}$  at the 95th percentile (or, 5% distribution) from the two sets (the two arrows extended to the y-axis). It also illustrates that the 95th percentile exposure of the Set 2 ("no cotton") would approximately be at the 97.5th percentile (or, 2.5% distribution) of the Set 1 ("with cotton") distribution (the arrow extended down to the x-axis from the "with cotton" exposure level at the 95th percentile).

Table 2. Bifenthrin Dietary Exposures based on 1989-91 CSFII consumption survey data <sup>a</sup>

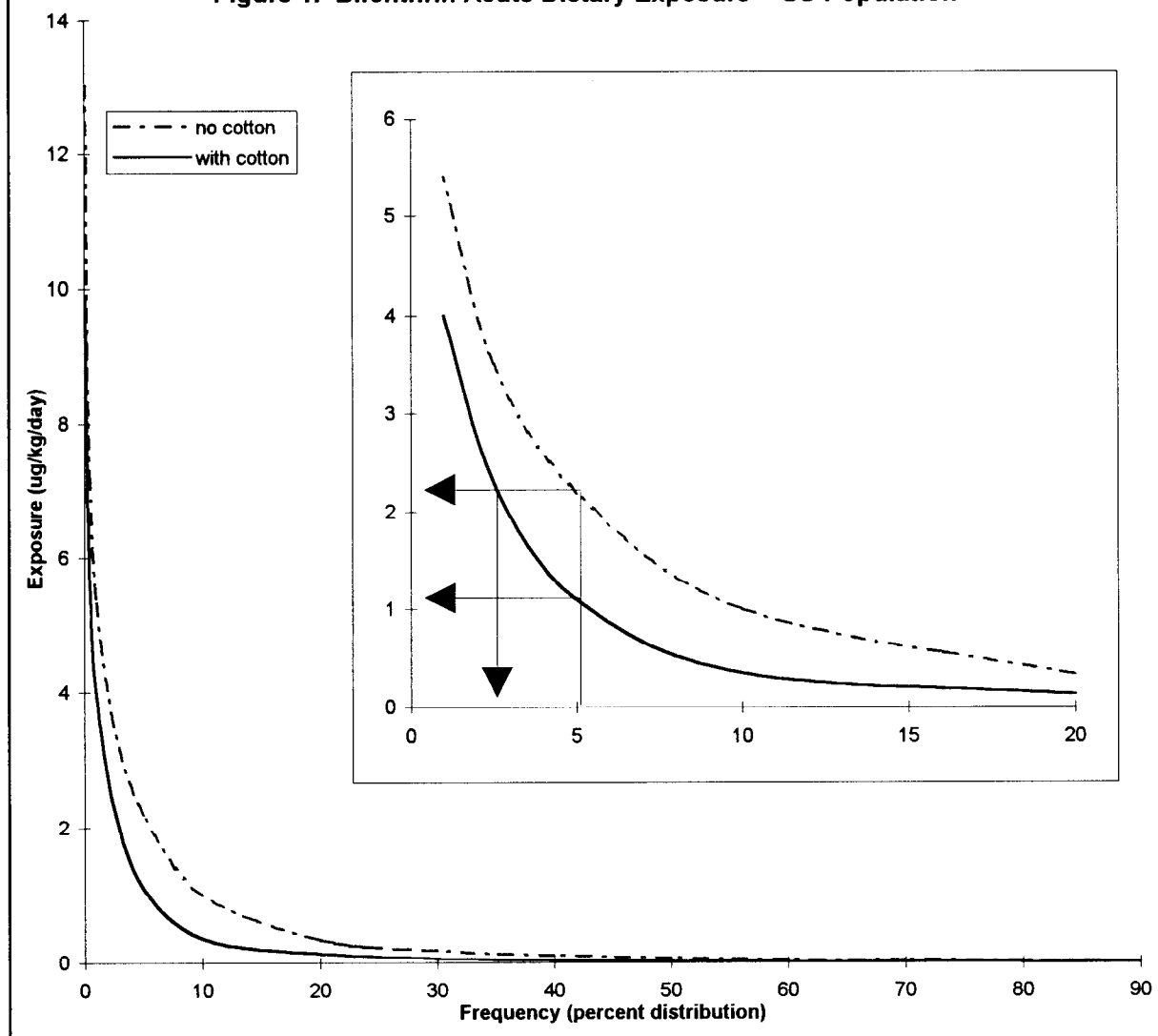
Population Subgroups	Acute Exposures <sup>b</sup> ( $\mu$ g/kg/day)		Chronic Exposures <sup>c</sup> ( $\mu$ g/kg/day)
	Set 1	Set 2	
US population	1.1	2.2	0.003
US population - Spring	0.84	2.0	0.003
US population - Summer	1.5	2.5	0.003
US population - Autumn	0.91	2.3	0.003
US population - Winter	0.88	2.2	0.003
Western Region	1.4	2.3	0.003
Hispanics	0.70	1.9	0.003
Non-Hisp. Whites	0.93	2.0	0.003
Non-Hisp. Blacks	1.6	3.3	0.003
Non-Hisp. Others	2.9	4.6	0.003
Nursing Infants < 1 yr	0.046	0.040	0.001
Non-Nurs. Infants < 1 yr	1.5	2.5	0.004
Females 13 + /Preg/non-nurs	0.59	1.2	0.002
Females 13 + /Nurs	1.2	3.5	0.002
Children 1-6 yr	1.1	3.5	0.007
Children 7-12 yr	0.59	1.3	0.005
Males 13-19 yr	0.61	2.1	0.004
Females 13-19 yr	0.52	2.3	0.003
Males 20+	1.1	2.0	0.003
Females 20+	1.4	2.4	0.002
Seniors 55+	1.8	2.7	0.002
All infants	1.6	2.4	0.003
Females 13-50	0.80	2.1	0.002

<sup>a</sup>/ CSFII: USDA 3 years data (1989-90 to 91-92) of Continuing Survey of Food Intakes by Individuals.

<sup>b</sup>/ The 95th percentile of the user-day for each population subgroup. Set 1 included the exposures from cotton products, meat and milk, and all the commodities for the FIFRA Section 18 (Emergency Exemption) use. Set 2 excluded cotton products and meat and milk.

<sup>c</sup>/ The average exposure for all person-day (total number of days all the persons were surveyed for consumption), including days that none of the commodities under analysis were consumed (i.e., zero exposures).

**Figure 1. Bifenthrin Acute Dietary Exposure - US Population**



The respective Set 2 acute exposures (no cotton) for males and females above 20 years old were 2.0 and 2.4  $\mu\text{g/kg/day}$  (Table 2). The average of the two values was 2.2  $\mu\text{g/kg/day}$ . This exposure level was taken as the acute exposures for adults and was combined with occupational exposures in estimating the total exposures of workers (Section III.B.).

### Lifetime exposures

The potential chronic dietary exposure was calculated using the Exposure-1 software program developed by TAS, Inc. (TAS, 1996b). The food consumption data for the chronic analysis were also based on the USDA CSFII survey data, combining the 3-year survey data (USDA, 1989-91). The program estimates the annual average exposure for all members of a designated population subgroup (Table 2). The lifetime weighted average exposure of 0.003  $\mu\text{g/kg/day}$  was calculated from the mean exposures from each population age group, using the following equation:

$$\text{Lifetime exposure} = \left(\frac{1}{70} \times E_1\right) + \left(\frac{5}{70} \times E_2\right) + \left(\frac{6}{70} \times E_3\right) + \left(\frac{7}{70} \times E_4\right) + \left(\frac{51}{70} \times E_5\right)$$

where:  $E_1$ ,  $E_2$ ,  $E_3$ ,  $E_4$ , and  $E_5$  were the age-specific chronic exposures:  
 $E_1$ : infants <1 year (0.025  $\mu\text{g/kg/day}$ ),  $E_2$ : children 1-6 years (0.007  $\mu\text{g/kg/day}$ ),  $E_3$ : children 7-12 years (0.005  $\mu\text{g/kg/day}$ ),  $E_4$ : males and females 13-19 years (0.0035  $\mu\text{g/kg/day}$ ), and  $E_5$ : adults at or beyond 20 years (0.0025  $\mu\text{g/kg/day}$ ).

## III.B. Occupational Exposures

The acute and lifetime average occupational exposures of mixer/loaders, applicators, and harvesters of greenhouse ornamental flowers were estimated using surrogate data and the data on bifenthrin dislodgeable residue from field trials. A detailed description of the assessment was presented in Dong (1996). Only a brief summary of the assessment is presented in this section. Two exposure estimates for each work task were given, the "average" and the "high" values. The total exposure of workers was the sum of the occupational and dietary exposures, with the dose from occupational exposures being adjusted to an equivalent oral exposure by the 28% oral absorption factor. The exposure estimates are given in Table 3.

### III.B.1. Acute exposure levels

Dermal exposure was considered the primary route of occupational exposures (Dong, 1996). Inhalation exposure, when compared to the exposure through dermal contact, was determined to be negligible for all work tasks, including application (Dong, 1996). The absorbed daily dosage (ADD) was estimated based on the dermal absorption factor of 17.9% and an average body weight of 68.7 kg.

#### Mixer/Loader

The exposures for mixing and loading were estimated from Pesticide Handlers Exposure Database (PHED). For workers wearing work clothes (long-legged trousers and a long-sleeved shirt) and gloves, the average exposure was 0.68 mg/day for each pound of liquid formulation used in an open pour loading operation. The average and high ADDs were calculated based on the respective assumption of average (0.6 lb/day) and high end (0.8 lb/day) of greenhouse use per day.

Table 3. Bifenthrin occupational and total exposures of workers associated with the use of Talstar® T&O<sup>a</sup>

Workers	Acute Exposure ( $\mu\text{g/kg/day}$ )			Lifetime Exposure ( $\mu\text{g/kg/day}$ )		
	ADD	Oral equiv. <sup>b</sup>	Total <sup>c</sup>	LADD	Oral equiv. <sup>b</sup>	Total <sup>c</sup>
Mixer/Loader						
Average	1.1	3.9	6.1	0.01	0.036	0.039
High	1.4	5.0	7.2	0.01	0.036	0.039
Applicator						
Average	61.0	217.9	220.1	0.2	0.714	0.717
High	156.3	558.2	560.4	2.7	9.643	9.646
Mixer/Loader/Applicator						
Average	62.1	221.8	224.0	0.2	0.714	0.717
High	157.7	563.2	565.4	2.7	9.643	9.646
Harvester						
Average	129.8	463.6	465.8	7.1	25.357	25.360
High	173.0	617.9	620.1	9.5	33.929	33.932

<sup>a</sup>/ Data taken from Dong (1996). ADD: Absorbed Daily Dose for occupational exposures; LADD: Lifetime Absorbed Daily Dose for occupational exposures. These values were estimated based on a dermal absorption factor of 17.9%.

<sup>b</sup>/ The oral equivalent occupational exposure was the occupational exposures (ADD or LADD) divided by the oral absorption factor of 28%.

<sup>c</sup>/ The total exposure is the sum of the oral equivalent exposure and the dietary exposure. The respective acute and chronic dietary exposure was 2.2 and 0.003  $\mu\text{g/kg/day}$ .



### Applicator

The exposure for an applicator was based on surrogate data from fluvalinate greenhouse applications to chrysanthemums and African violets by two male and two female workers. The estimated average and high-end exposure was 23.4 and 60 mg/kg respectively for each pound of active ingredient (a.i.) applied. The average exposure was calculated based on the average exposure (i.e., 23.4 mg/lb a.i.) and the assumption of an average single day application of 300 gallons spray solution (i.e., 0.6 lb bifenthrin). The high-end exposure was calculated based on the high-end exposure (i.e., 60 mg/lb a.i.) and the assumption of a high-end single day application of 400 gallons spray solution (i.e., 0.8 lb bifenthrin).

### Harvester

The harvester exposure was calculated as the level of dislodgeable foliar residue (DFR) multiplied by the dermal transfer factor (TF). Data for DFR were taken from a study with 1 to 3 applications of bifenthrin to chrysanthemums and roses. The results showed no appreciable decline in foliar residues within 3 weeks. Without a label specification for a maximum number of application, a maximum of 4 applications was assumed because it was expected that the highest residue level would be attended after 4 successive applications (Dong, 1996). The estimated DFR after 3 or 4 applications was 0.9 or 1.2 ug/cm<sup>2</sup> respectively, based on the DFR of 0.3 ug/cm<sup>2</sup> after 1 application. The TF of 7,000 ug/hr per unit DFR (i.e., ug/cm<sup>2</sup>) was estimated based on the exposures of greenhouse workers harvesting carnations and roses that had been treated with chlorothalonil and thiophanate-methyl. The exposures were calculated based on 8 hours of work per day.

### III.B.2. Lifetime exposure levels

The toxicological endpoint for long-term exposures is oncogenicity. The current operational default assumption for conducting oncogenicity risk assessment is that the risk is proportional to the daily exposure averaged over a lifetime. Therefore, the LADD was estimated for each work task. The estimated exposure levels are also presented in Table 3.

### Mixer/Loader

The average and high estimates of the LADD were calculated from the average and high ADD of 1.1 and 1.4 µg/kg/day, respectively. The exposure frequency was assumed to be at an average of 10 days per year and a total of 10 years in a 75 year lifetime.

### Applicator

The average and high estimates of the LADD were calculated from the average and high ADD of 61.0 and 156.3 µg/kg/day, respectively. The exposure frequency was assumed to be 10 days per year for the average exposure and 48 days per year for the high end of exposure. The LADD was calculated based on 10 years of exposure in a 75 year lifetime.

### Harvester

The average and high estimates of the LADD were calculated from the average and high ADD of 129.8 and 173 µg/kg/day, respectively. The exposure frequency was assumed to be 150 days per year and a total of 10 years in a 75 year lifetime.

#### IV. RISK CHARACTERIZATION

The risk of acute exposures was characterized by the margin of exposure (MOE). The MOE is the ratio of the NOEL over the exposure. The risk from chronic, long-term exposures was characterized by the quantitative risk estimate. It was calculated as the product of potency value multiplied by the lifetime average daily exposure. A summary of the MOEs and risk estimates are given in Table 4.

Table 4. The risk of total (occupational and dietary) bifenthrin exposure of workers associated with the use of Talstar® T&O<sup>a</sup>.

Workers	Acute Risk		Lifetime Oncogenic Risk	
	Exposure ( $\mu\text{g/kg/day}$ )	MOE <sup>b</sup>	Exposure ( $\mu\text{g/kg/day}$ )	Risk <sup>c</sup>
Mixer/Loader				
Average	6.1	160	0.039	$1 - 2 \times 10^{-6}$
High	7.2	140	0.039	-----
Applicator				
Average	220.1	5	0.717	$2 - 3 \times 10^{-5}$
High	560.4	2	9.646	$3 - 4 \times 10^{-4}$
Mixer/Loader/Applicator				
Average	224.0	5	0.717	$2 - 3 \times 10^{-5}$
High	565.4	2	9.646	$3 - 4 \times 10^{-4}$
Harvester				
Average	465.8	2	25.360	$7 - 11 \times 10^{-4}$
High	620.1	2	33.932	-----

<sup>a</sup>/ The total bifenthrin exposure of workers includes the dietary exposures to bifenthrin from the use of Capture® 2EC and the occupational exposure associated with the use of Talstar®T&O.

<sup>b</sup>/ The MOE (margin of exposure) was calculated as the ratio of the NOEL (1 mg/kg/day) over the exposure.

<sup>c</sup>/ The lifetime oncogenic risk was calculated as the product of potency multiplied by the exposure. The given risk levels ranged from the maximum likelihood estimate (MLE) to the 95% upper confidence bound (UB), using the MLE potency of  $2.6 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$  and its UB of  $4.3 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$ .

#### IV.A. Acute Exposures

The MOE calculated for the acute exposure of workers was based on the oral NOEL of 1.0 mg/kg/day established in pregnant rats, in which tremors were observed in rats at the LOEL of 2.0 mg/kg/day. The MOEs for the mixer and loader were 140-160. A MOE of at least 100 is generally considered protective of human health when the adverse effects are based on animal data. The MOE of 100 takes into account both the interspecies and the inter-individual variation of sensitivity. In extrapolating data from animals to humans, it is usually assumed that humans could be 10 times more sensitive than laboratory animals. In considering the heterogeneity in human population (e.g., genetic predisposition, age, life style), it is assumed that the inter-individual differences in sensitivity to a chemical toxicant could be as much as 10-fold.

The MOEs for workers performing the tasks of Talstar® application or harvesting cut flowers treated with Talstar® were 5 to 2. For these workers, dietary exposures contributed less than 1% to the total exposure (Table 3) and were considered insignificant.

#### IV.B. Lifetime Oncogenic Risk

The potential lifetime oncogenic risk of workers was calculated based on the estimated average LADD. A lifetime oncogenic risk was not calculated based on the "high" exposure estimates for mixer/loaders and harvesters. This is because they were estimated from the "high" ADD acute exposures (i.e., high ADD), with the same exposure parameters (i.e., number of days per year and years per lifetime of exposures) as for the average LADD. It is unlikely that the daily "high" exposures would occur repeatedly for all exposures in a lifetime. On the other hand, the risk of applicators, with or without the tasks of mixing and loading, was presented for both the average and high exposures. Although the high LADDs were also calculated from the high ADDs, different lifetime exposure parameters were used in their calculations. The average and high LADD were calculated based on 10 and 48 days per year of exposures, respectively. It would have been more realistic to calculate the high LADD using the average ADD rather than the high ADD, a lowering of the LADD by approximately 2.6-fold.

The risk for mixer/loaders was the lowest, with the lifetime probability of oncogenic effects ranging from 1 to  $2 \times 10^{-6}$ . The risk was highest for the harvesters, ranging from  $7-11 \times 10^{-4}$ , or 7-11 in 10,000. The risk of applicators ranged from  $2-3 \times 10^{-5}$  to  $3-4 \times 10^{-4}$ . As shown in Table 3, dietary exposures contributed less than 1% to the total lifetime exposures for all workers.

### V. RISK APPRAISAL

The risk of Talstar® exposures was characterized for the acute and potential lifetime exposures. Uncertainties are introduced into the risk assessment through each component of the risk assessment. When sufficient data were not available, default assumptions were used. Some areas of uncertainty specific to the risk assessment of Talstar® are presented below.

The most sensitive clinical signs of toxicity that formed the basis for the determination of a critical NOEL were tremors observed in laboratory animals. A critical oral NOEL of 1 mg/kg/day was used in the calculation of MOE because of the uncertainties in the dermal studies for establishing a critical NOEL. Additionally, uncertainties also exist when typical dermal studies are used in assessing the risk of human exposures, especially when no pharmacokinetic data are available for adjusting the absorption factor between the high concentration over smaller surface area in animal studies and the lower concentration over larger surface area experienced in human exposures (section II.B.2.). On the other hand, uncertainty also exists when an oral NOEL is

used to calculate the MOE of an exposure that is mostly dermal. Therefore, a quantitative comparison between the outcome (i.e., MOE) of using either the oral or the dermal NOELs may be beneficial for providing a boundary for the assessment. In this comparison, it should be understood that the scientific basis for the comparison is by no means firmly established. As discussed in section II.B.2., the absorption-adjusted oral and dermal NOELs differed by 16- to 32-fold. Assuming that rabbits in the dermal studies may be up to 3-fold less sensitive than rats (section II.B.3.), and that pregnant rats may be up to 2.5-fold more sensitive than non-pregnant rats (section II.B.1), the adjusted dermal NOEL could then be approximately 2- to 4-fold higher than the oral NOEL. This would consequently bring the lowest MOE of 2 - 5 for harvesters and applicators up to 4 - 20. A detailed discussion on the uncertainty in assessing the risks based on a dermal NOEL was presented in Section II.B.2.

Uncertainty exists in the oncogenicity data. Dose-response data obtained from animal bioassays at substantially high dose levels were extrapolated downward by orders of magnitude to low dose ranges experienced in human exposures. With no data for characterizing the extrapolation, a default of linearity at the low-dose range was assumed. There was also uncertainty regarding the incidence of urinary bladder tumors which formed the basis for the extrapolation. Nevertheless, the current data were not sufficient for a refinement of the assessment.

There were also several areas of uncertainty in the exposure assessment. One area of uncertainty relates to the exposure parameters (e.g., amount of use; hours per day, days per year, years per lifetime). The other area of uncertainty was the use of surrogate data (e.g., data from PHED, surrogate TF, etc) instead of data specific collected from bifenthrin applications and uses. Since the LADD was calculated from the ADD with the presumed frequency of work activities (annual and lifetime) (section III.B.2), any changes in the ADD would proportionally change the LADD and hence, the risk estimates. Detailed discussions on the source of data and the assumptions used were given in Dong (1996).

Bifenthrin also caused erythema at the site of contact in rabbits when applied dermally. The critical NOEL for local effects was estimated as 2.5 mg/kg. A more appropriate unit for this dose would be the amount of bifenthrin per unit area rather than per unit body weight. However, the available toxicological data did not permit the dose quantitation per unit area. The exposure estimates as presented by Dong (1996) were also not in the dose unit (i.e., weight per surface area) for characterizing the risk of skin effects. Local dermal toxicity might be an area for further investigation since the current illness report appeared to indicate that skin effects may be a potential area of concern.

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